REMARKS

Status of the Claims

Claims 1, 3-6, 8, 9 and 16 are pending. Claims 1, 3-6, 8, 9 and 16 are rejected.

Claims 1 and 8 are amended. Claim 16 is canceled. Withdrawn claims 10-15 are canceled herein.

Amendments to the claims

Claim 1 has been amended and now recites a method of inducing systemic tolerance to an antigen in an individual in need of such treatment, comprising the step of: administering to the individual antigen presenting cells which (1) express high levels of Fas ligand resulting from co-infection with AdLoxPFasL and AxCANCre adenoviruses, (2) do not express Fas and (3) express antigen, where the antigen presenting cells induce apoptosis of Fas-positive T-cells directed towards the antigen resulting in the induction of systemic tolerance to the antigen.

Further, Claim 8 has been amended and now recites a method of claim 1, further comprising the step of delivering *in vitro* to the antigen presenting cells a gene to inhibit apoptosis.

The 35 U.S.C. §112 first Paragraph Rejection

Claims 1, 3-6, 8-9 and 16 are rejected under 35 U.S.C 112, first paragraph, since the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly

connected, to use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

The Examiner states the following reasons for rejecting claims 1, 3-6, 8-9 since it would require undue experimentation to practice the scope of the claim as written: (1) they recite use of any Fas negative antigen presenting cells infected with AdLoxFasL and AxCANCre to induce systemic tolerance when the specification discloses the use of only peritoneal macrophages; and (2) teachings of the prior art (**Restifo** (2000) Nature Med., Vol. 6(5), 493-495, **Kang et al.** (1998) Trans. Proceed Vol 30, 538, **Seino et al.**(1997) Trans. Proceed. Vol 29, 1092-1093) that ectopic expression of Fas ligand on cells results in inflammation and not immunesuppression.

Applicants contend that the present invention is different and distinct from cited prior art references and that the problem posed by the prior art references is not applicable to the claimed invention. Although the prior art references and the present invention investigate Fas ligand based immunotherapy, these references differ in the techniques that were used. Firstly, the present invention teaches the use of antigen presenting cells (APCs),

which can be loaded with antigen that can be processed and presented to T cells. This is important since T cells are relatively resistant to Fas ligand induced apoptosis unless they are stimulated by specific antigen and encounter Fas ligand, both of which in the present invention is present on antigen presenting cells. Secondly, these antigen presenting cells are Fas negative which ensures protection of these cells from apoptosis once they express Fas ligand. Thirdly, antigen presenting cells in the present invention were infected using AdLoxPFasL and AxCANCre adenoviruses that enables high levels of Fas ligand expression in addition to controlling the expression of Fas ligand (Example 19). Fourthly, the use of antigen presenting cells enables targeting of Fas ligand to the precise site where they are able to induce maximum benefit toward interaction with autoreactive T cells. Additionally, the specification provides ample guidance to one skilled in the art regarding the construction of Fas ligand expressing adenovirus vectors (Example 2) to experiments that can be performed to assess the induction of tolerance *in vivo* by these Fas-ligand expressing vectors (Examples 16-23).

In distinct contrast, none of the cited prior art references teach the use of "Fas negative antigen presenting cells" nor do they teach "transduction with combined adenoviruses" as described in the present invention. Therefore, it is unreasonable to state that based on the data cited in the prior art, the skilled artisan would have expected inflammation and not immunosuppression after transplantation of cells modified to express Fas ligand. In fact, Example 18 of the present invention addresses the issue of infammation and teaches that the Fas ligand expressing antigen presenting cells migrated to lymphoid organs and induced apoptosis of T cells. Additionally, it also teaches that liver damage, which is seen on systemic administration of soluble Fas ligand or anti-Fas antibody was not observed on administration of these antigen presenting cells. Therefore, the scope of amended claim 1 is commensurate with the scope of the enablement provided in the specification. Accordingly, based on these remarks Applicants respectfully request the withdrawal of rejection of claims 1, 3-6, 8 and 9 under 35 U.S.C 112, first paragraph.

The Examiner states following reasons for rejecting claim 16 since it would require undue experimentation to practice the scope of the claim as written: (1) teachings of prior art (**Zhang et al.** (1998) J.Virol., Vol. 72(3), page 2484, col. 1; **Murave et al.**, (1997) Human Gene Ther., Vol. 8, page 960, col. 2) that expression of Fas ligand in cells that already express Fas results in apoptosis of the transfected cell itself; (2) teachings of the prior art (**Restifo**, **Kang et al.**, **Seino et al.**) that transplantation of cells expressing Fas ligand does not grant immune privilege as the cells are rapidly rejected; (3) lack of evidence in the specification that transplantation of any Fas ligand expressing cell can result in promoting T cell tolerance or immune privilege in vivo. Claim 16 has been cancelled. Accordingly, the 35 U.S.C. 112, first paragraph rejection of claim 16 is moot.

Regarding claims 8 and 9, the Examiner states the following reasons for their rejection since it would require undue experimentation for the skilled artisan to deliver a gene to a specific set of transplanted antigen presenting cells in vivo by direct administration of any vector encoding the gene: (1) teachings of

prior art (**Deonarain et al.** (1998) Exp. Opin. Ther. Patents, Vol. 8(1), page 53, lines 1-4 and page 54, lines 12-15; **Miller et al.** (1995) FASEB, Vol. 9, page 198, paragraph 2) that achieving targeted delivery in vivo is unpredictable; (2) lack of guidance provide by the specification for targeting delivery of a gene to transplanted antigen presenting cells in vivo. Applicants respectfully traverse this rejection.

Claim 8 has been amended and now recites a method of in vitro delivery of gene that inhibits apoptosis to antigen presenting cells. Therefore, the scope of the amended claim 8 is commensurate with scope of the enablement provided in the specification. Accordingly, based on the amendments and remarks, Applicants respectfully request the withdrawal of rejection of claims 8 and 9 under 35 U.S.C 112, first paragraph.

Accordingly, based on the amendment and remarks, Applicants respectfully request the withdrawal of rejection of claims under 35 U.S.C 112, first paragraph.

The 35 U.S.C. §112, Second Paragraph, Rejection

Claims 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner states that claim 1 contains a grammatical error that renders the claim confusing. The Examiner specifically points out to the error in line 5 of claim 1, which recites "...(1) express high level of fas ligand resulted from co-infection..." and suggest the following amendment to overcome the rejection: "...(1) express high levels of fas ligand resulting from co-infection...". Applicants respectfully traverse this rejection.

Claim 1 has been amended. Accordingly, based on the amendment and remark, Applicants respectfully request the withdrawal of rejection of claim 1 under 35 U.S.C. 112, second paragraph.

This is intended to be a complete response to the Office Action mailed May 18, 2004. Applicants submit that the pending

claims are in condition for allowance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

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